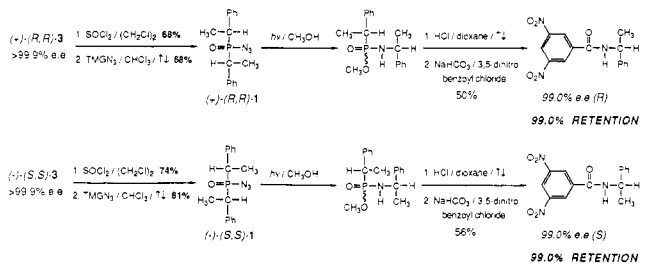
Scheme IV



(R,S)-**3**[12a] (mp 157–158 °C), which has been synthesized by an independent route.[13] Unfortunately, the resolution of the desired diastereomers required extensive and sacrificial purification, which afforded only **2d** in sufficient quantities for further studies. However, a sample of **2c** provided a crystal suitable for X-ray structure analysis,[14] which allowed assignment of the absolute configurations of **2c** and **2d** as S,S and R,R, respectively. Acidic hydrolysis of **2d** afforded a dextrorotatory acid (+)-(R,R)-**3**[12b] ($[\alpha]^{30}_{405}$ +45.8°, mp 192 °C), which was shown to be of >99.9% ee by HPLC analysis[10b] of a derived 2,4-dinitroanilide.[12c]

The enantiomeric acid could be obtained in larger quantities by a similar resolution sequence using (R)-methylphenylglycinate (>99.9% ee[10a]) as shown in Scheme III.[15] In this case the desired diastereomer, **4c**,[12a] could be separated from **4d**,[12a] but it was always contaminated with traces of **4a** (1.2%). Acidic hydrolysis of **4c** provided a levorotatory acid (−)-(S,S)-**3**[12c,d] ($[\alpha]^{29}_{405}$ −45.4°, mp 192–192.5 °C). The meso contaminants were easily removed at the azide stage.

The phosphinic azides (R,R)-**1**[12b] and (S,S)-**1**[12c,d] were prepared by conversion of the acids to the (R,R)-[12b] and (S,S)-phosphinic chlorides[12c,d] followed by treatment with tetramethylguanidinium azide ($TMGN_3$) (Scheme IV). The chiral azides were assumed to have the same ee as the starting acids since no epimerization was detected as indicated by the absence of meso azides.

The phosphinoyl photo-Curtius rearrangements were performed by irradiation of the azides in methanolic solution at 254 nm. The concentrated photolysate containing a mixture of the P-epimeric phosphonamidates was hydrolyzed with acid, and the 1-phenylethylamine released was isolated by derivatization as the 3,5-dinitrobenzamide under Shotten–Baumann conditions (overall yield 50–56%).[16] HPLC analysis of the 3,5-dinitrobenzamide from the rearrangement of (R,R)-**1** showed a 99.0% ee of (R)-1-phenylethylamine while the product of rearrangement of (S,S)-**1** showed an identical 99.0% ee of the (S)-antipode. Since both starting azides were enantiomerically pure, this corresponds to migration of the carbon center with *99.0% net retention of configuration.* These results accord well with the classic studies by Kenyon[17] on the stereochemical course of migration in the thermal Curtius rearrangement of acyl azides, which also occurs with nearly complete retention of configuration. The photo-Curtius rearrangement of acyl azides has not been explicitly stereochemically defined, but retention of configuration has been documented in isolated cases.[18]

The demonstrated ability to selectively excise the phosphorus unit provides great impetus for the development of chiral prosthetic groups, which will control the creation of C–C single bonds next to the phosphorus. This also serves to illustrate one of the important advantages of phosphorus compared to sulfur-based methods. We are extending these studies to establish the stereochemical detail in the base-induced Lossen rearrangement of phosphinoyl hydroxylamines[19] and dyotropic rearrangement of phosphinic peroxides.[20] In addition, we will be investigating the corresponding reactions in a *phosphonic* model system.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. This work was supported in part by the University of Illinois Mass Spectrometry Laboratory (PHS HHS GM-27029). We thank Professor William H. Pirkle for assistance with the HPLC analyses. Dr. Scott R. Wilson is gratefully acknowledged for the X-ray structure determination of **2c**. S.E.D. acknowledges the A. P. Sloan Foundation for a Fellowship (1985–1989).

Supplementary Material Available: Full characterization data for (+)-**1**, (−)-**1**, **2a–d**, (+)-**3**, (−)-**3**, and **4b–d** is provided along with a procedure for the phosphinoyl photo-Curtius rearrangements of (+)-**1** and (−)-**1** (12 pages). Ordering information is given on any current masthead page.

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(13) Dorow, R. L., unpublished results from these laboratories.
(14) Refinement of the crystallographic analysis was extremely difficult due to the presence of four molecules in each unit cell (space group P_1) in different conformations.
(15) Due to chromatographic coincidences it was not possible to obtain both antipodes from a single resolution method.
(16) Control experiments showed that no isomerization occurred after the rearrangement.
(17) (a) Kenyon, J.; Young, D. P. *J. Chem. Soc.* **1941**, 263. (b) Campbell, A.; Kenyon, J. *Ibid.* **1946**, 25.
(18) (a) ApSimon, J. W.; Edwards, O. E. *Can. J. Chem.* **1962**, *40*, 896. (b) Meyer, W. L.; Levinson, A. S. *J. Org. Chem.* **1963**, *28*, 2859. (c) Brown, R. F. C. *Aust. J. Chem.* **1964**, *17*, 47.
(19) Harger, M. J. P.; Smith, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 683 and references cited therein.
(20) Dannley, R. L.; Waller, R. L.; Hoffman, R. V.; Hudson, R. F. *J. Org. Chem.* **1972**, *37*, 418.

Anthrones as Reactive Dienes in Diels–Alder Reactions

Summary: Anthrone and related phenols and hydroquinones exhibit solvent-dependent high diene reactivity in Diels–Alder reactions; evidence for a catalytic oxyanion accelerated pathway is presented.

Sir: In order to be of maximum value as an olefin protecting group, a 1,3-diene must: (1) exhibit high Diels–Alder reactivity; (2) form cycloadducts that are not readily degraded by functional-group interconversions; and (3) give cycloadducts that undergo facile retro-Diels–Alder reactions under specific conditions. Anthracenes meet the second requirement well, as first illustrated by Diels and Thiele in 1938.[1] Recently Knapp et al.[2] demonstrated very

(1) Diels, O.; Thiele, W. E. *Chem. Ber.* **1938**, *71*, 1173; we wish to thank a referee for pointing out this early example. The use of arenes in cycloaddition reactions is the subject of a review: Wagner-Jauregg, T. *Synthesis* **1980**, 165.

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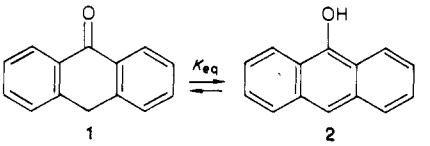
facile bridgehead oxyanion accelerated retro-Diels–Alder reactions of anthracene cycloadducts, and Czarnik et al.[3] have reported enhanced retro-Diels–Alder rates for bridgehead diol- and diaminoanthracene adducts, suggesting a general solution to the third requirement. Given these desirable features, it is especially unfortunate that anthracene exhibits only modest reactivity in cycloaddition processes.

This reactivity can be enhanced by linear benzannulation, as quantified in the work of Biermann and Schmidt[4] for the reaction of maleic anhydride (MA) with a large number of polycyclic aromatic hydrocarbons. In principle, enhanced cycloaddition reactivity can also be conferred by substituents, although the results of Sauer and Wiest[5] on the effects of methoxy groups are not encouraging in this regard. In cycloaddition with MA, 9-methoxyanthracene is only 2.5 times more reactive than anthracene itself, and the rate of 9,10-dimethoxyanthracene is actually depressed (k_{rel} = 0.29). Also, we have found that the 9-methoxymethyl ether of anthracene is somewhat less reactive than anthracene itself with *N*-methylmaleimide (NMM) in various solvents.[6]

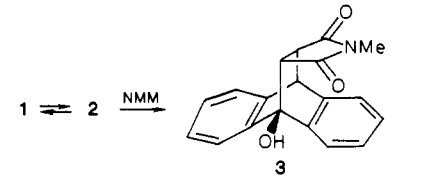
Before abandoning efforts with the anthracene ring system, it was decided to explore the use of anthrone (9-(10*H*)-anthracenone, **1**) as a masked diene. Remarkably, **1** was found to react with NMM in the solvents dimethylformamide[7] (DMF), pyridine, or Et_3N *at least* 10^4 *times faster than anthracene.* Although anthrone has been used previously as the diene component in Diels–Alder reactions, specifically with ethylene,[8] dimethyl acetylenedicarboxylate,[9] and MA,[9] its unusual reactivity apparently has not been recognized.

The equilibrium position between the tautomers anthrone (**1**) and anthracenol (**2**) is known to be strongly solvent dependent. K_{eq} values in different media have been determined by Mills and Beak.[10] The keto form **1** is strongly favored in nonpolar solvents, whereas hydrogen bond acceptor[11] solvents cause **2** to be slightly preferred.



1 2 (1)

Conceivably reflecting these differences, slow reaction (14% cycloadduct formed in 68 h, 25 °C, k = ca. 10^{-5} M^{-1} s^{-1}, assuming second-order rate-determining cycloaddition[12]) was observed for a solution of anthrone and NMM (0.10 M each; 25 °C) in $CDCl_3$ ($K_{eq} \leq 10^{-3}$ in $CHCl_3$).[10] In DMF (K_{eq} = 1.3 ± 0.1)[10] this reaction is complete within a few minutes ($k \geq 0.3$, using the same assumptions), as judged by the NMR spectrum of a vacuum-pumped aliquot taken shortly after mixing. The reaction is also very rapid in pyridine (K_{eq} = 1.4 ± 0.5)[10] and in triethylamine (K_{eq} = 1.1 ± 0.5).[10] The cycloadduct **3** is formed quantitatively in each of these solvents.



3 (2)

It was established that **3** is formed irreversibly in DMF. A mixture of **3** and 1,3-diphenylisobenzofuran stirred for 3 days at room temperature gave no evidence (NMR) of the formation of the stable NMM adduct of the latter diene.

The greater equilibrium concentration of **2** could account for the higher rate in DMF relative to $CDCl_3$, but it does not provide a rationale for the difference between anthrone and anthracene (or 9-methoxyanthracene) in polar solvent. The reaction of anthracene with NMM in DMF at 25 °C has k = ca. 10^{-5} M^{-1} s^{-1}, at least 10^4 slower than the reaction with anthrone. The poorer[13] dienophile dimethyl fumarate was used in an effort to obtain another estimate of this rate difference. With this reagent anthrone cycloaddition (DMF, 25 °C) occurred at a moderate rate (k = 2.2 × 10^{-3} M^{-1} s^{-1}), while neither anthracene nor 9-methoxyanthracene gave measurable (NMR) cycloadduct after 148 h ($k \leq 2 \times 10^{-6}$ M^{-1} s^{-1}). Thus enhanced rates are not restricted to NMM but are also observed with dimethyl fumarate (≥10^3), and even methyl acrylate has been found

(2) Knapp, S.; Ornaf, R. M.; Rodrigues, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 5494. A fairly reactive dienophile (benzoquinone) was used in the initial cycloaddition step.

(3) Chung, Y.-S.; Duerr, B. F.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1988**, *53*, 1336.

(4) Biermann, D.; Schmidt, W. *J. Am. Chem. Soc.* **1980**, *102*, 3163. The relative rates of cycloaddition of anthracene, naphthacene, and pentacene with maleic anhydride are 1, 42, and 720, respectively, in 1,2,4-trichlorobenzene solvent at 91.5 °C.

(5) Sauer, J.; Wiest, H. *Angew. Chem., Int. Ed. Engl.* **1961**, *1*, 269; the most reactive derivative was 9,10-dimethylanthracene, which had k_{rel} = 218; (k_{rel} = 1 for anthracene).

(6) NMM and MA are similar in reactivity, with one or the other being more reactive, depending upon the diene and conditions employed; with anthracene in refluxing chlorobenzene, NMM is faster than MA by a factor of ca. 3. We prefer NMM as a test dienophile because its cycloadducts are relatively stable toward hydrolysis, and the *N*-Me group is useful for NMR analyses. The k_{rel} for 9-OMOM anthracene (vs anthracene) with NMM varied from 0.36 ($CDCl_3$, 25 °C) to 0.8 in refluxing chlorobenzene (131 °C), as determined by the competition kinetics method.

(7) The DMF used in this study was Fisher Scientific reagent grade material, stored over 3A molecular sieves. The rates of anthrone reactions in DMF appear to be dependent on the source and history of DMF employed, as one would expect from catalysis by impurities such as dimethylamine, but this feature has not been examined closely.

(8) Meek, J. S.; Evans, W. B.; Godefroi, V.; Benson, W. R.; Wilcox, M. F.; Clark, W. G.; Tiedeman, T. *J. Org. Chem.* **1961**, *26*, 4281; the reaction with ethylene was carried out at temperatures of ca. 200 °C in dioxane/aqueous NaOH or (better yield) in pyridine. The authors viewed the reaction as proceeding through the salt (anion) of 9-anthracenol and even attempted (without success, in aqueous medium) to carry out a base-induced retro-Diels–Alder reaction of the cycloadduct (cf. ref 2). In the absence of base, in toluene solvent, a poor yield of adduct was obtained, along with several other products. The temperatures used for the anthrone reactions were like those used for cycloadditions of other 9-substituted anthracenes with ethylene, although it was not clearly established that high temperature was required for anthrone. For related work involving the 9-OMe and 9-OAc anthracenes with various activated dienophiles, see: Meek, J. S.; Monroe, P. A.; Bouboulis, C. J. *J. Org. Chem.* **1963**, *28*, 2572.

(9) Cohen, D.; Millar, I. T.; Richards, K. E. *J. Chem. Soc. C* **1968**, 793; in contrast to Meek's work,[8] which involved basic conditions, reactions with DMAD and MA were carried out in refluxing acetic acid.

(10) Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216. See also: Almdal, K.; Eggert, H.; Hammerich, O. *Acta Chem. Scand.* **1986**, *B40*, 230.

(11) The Kamlet–Taft "hydrogen bond acceptor basicities" follow the order pyridine < triethylamine ≤ DMF, but all three are good acceptors: Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377.

(12) Rate constants were calculated using the equation $d[prod]/dt = k[anthrone][dienophile]$; those involving few data points are mentioned simply to provide a numerical context for the rate effect. The correct rate expression may be considerably more complex and solvent dependent and requires additional study.

(13) With cyclopentadiene, NMM reacts 53 times faster than dimethyl fumarate (in dioxane, 20 °C): Sauer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, *97*, 3183.

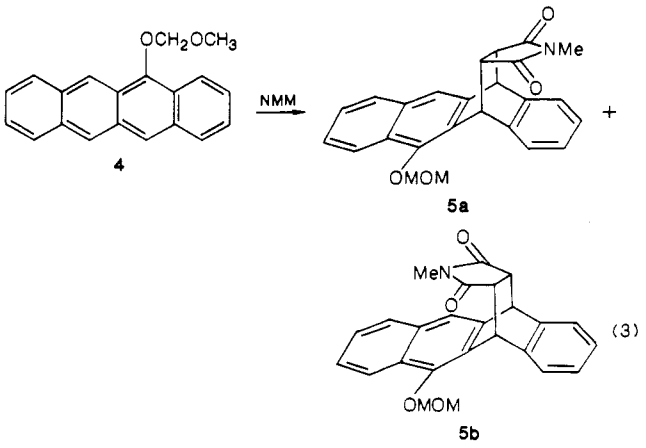
to give facile Et_3N-catalyzed cycloaddition at 25 °C when the dienophile is employed as solvent.

Catalytic[14] oxyanion acceleration can explain many observations made in this study. For example, the recalcitrant NMM + anthrone reaction in $CDCl_3$ was complete within the few minutes needed to obtain an NMR spectrum when a small amount (9 μL, ca. 1 equiv added to 1 mL of $CDCl_3$) of Et_3N was introduced. Similar behavior was observed in THF solvent. If it is assumed that the low concentration of Et_3N used does not significantly affect K_{eq}, this constitutes good evidence for base catalysis in these solvents. In keeping with this view, the addition of 2 equiv of DMF to THF did not measurably alter the very slow rate.

Reactions of anthrone in DMF may be catalyzed by traces of base, or the solvent itself may cause dissociation and allow rapid reaction via the oxyanion. An attempt to slow NMM cycloaddition by addition of 3 equiv of HOAc to the DMF solution failed to prevent the usual complete reaction within a few minutes. However, the addition of ca. 1 equiv of concentrated aqueous HCl slowed the cycloaddition. The reaction of anthrone with dimethyl fumarate is only slightly faster ($k = 6.4 \times 10^{-3}$ M^{-1} s^{-1}) in pyridine-d_5 than in DMF.[7] Addition of a small amount of Et_3N to the pyridine-d_5 solvent does not materially alter the rate ($k = 6.7 \times 10^{-3}$ M^{-1} s^{-1}). While some of these observations do not add support to the proposed oxyanion accelerated mechanism, neither do they negate this possibility.

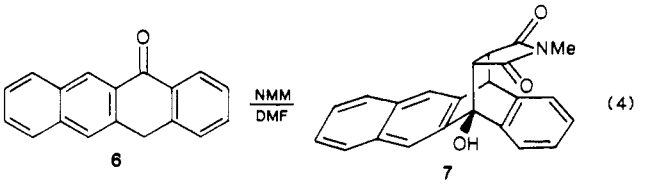
Refluxing acetic acid has been used as the solvent in an earlier cycloaddition application of anthrone,[8] and it was of interest to compare the reactivity of anthrone with that of anthracene in this medium. A competition experiment was carried out by adding 1 equiv of NMM to a refluxing solution of anthrone and anthracene (1 equiv each). After 40 min (and after 18 h), the mixture was cooled, and the volatiles were removed under vacuum; NMR analysis indicated that the NMM had been consumed, and the anthracene cycloadduct was the major product formed; the ratio of adducts (anthracene)/(anthrone) was 70/30. The anthrone/anthracenol K_{eq} has apparently not been determined in HOAc, and so this result cannot be used to calculate a meaningful rate ratio. Low anthracenol concentration may be responsible for the apparently diminished rate of anthrone relative to anthracene in this solvent, but the important qualitative observation is that the very large rate advantage enjoyed by anthrone in DMF and basic solvents is not evident in HOAc.

Another interesting feature emerged when napthacene analogues were examined. The very air-sensitive methoxymethyl ether **4**, like naphthacene itself, reacts readily with NMM at room temperature in $CHCl_3$ solvent. However, the major products arise from cycloaddition to the unsubstituted internal ring to give **5a,b** (stereoisomer identification has not been completed).



4 5a 5b (3)

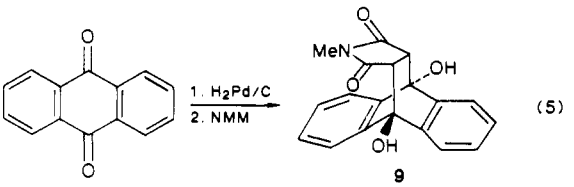
In contrast, 5(12*H*)-naphthacenone (**6**) in DMF gives the bridgehead hydroxyl NMM cycloadduct (**7** and its endo isomer) exclusively. This result is encouraging for prospective extension to very poor dienophiles, although it remains to be seen if the OH substituent effect is attenuated in **6** and higher benzologues.



6 7 (4)

Attention was next turned to the related diols. Anthraquinones are readily reduced under catalytic hydrogenation conditions to give anthracenediols. These air-sensitive hydroquinones (tautomers of hydroxyanthrones) have not been used previously as dienes in Diels–Alder reactions.[19]

Hydrogenation (Pd/C) of anthraquinone (**8**) in pyridine solvent, followed by addition of NMM, gave cycloadduct **9**. The same product was formed when a mixture of **8** and NMM in pyridine was subjected to H_2/Pd. Thus both the reduction of the quinone and the cycloaddition with NMM occur more rapidly than competing reduction of NMM, although any excess NMM is reduced to *N*-methylsuccinimide.



8 9 (5)

(14) The term *catalytic oxyanion acceleration* (base *catalyzed*) is used to distinguish this mechanism from oxyanion accelerated processes,[2,15] in which educts and adducts exist as the anions (base *induced*). Educts are favored thermodynamically on pK_a grounds in known oxyanion accelerated (base *induced*) retro-Diels–Alder reactions. In contrast, in a *catalyzed* process the oxyanion is an intermediate. The present work appears to provide the first example of a base-*catalyzed* Diels–Alder reaction. Czarnick and co-workers[3] have suggested that the retro-Diels–Alder reaction of a 9,10-dihydroxyanthracene cycloadduct may occur via the oxyanion; microscopic reversibility would then require that this particular Diels–Alder reaction also be viewed as a base-catalyzed process, even though at the high temperature employed the educts may be favored. It is noteworthy that Schulz and Frey[16] found that the addition of a small amount of lithium methoxide allowed the cycloaddition of 1,8-dihydroxy-9-anthrone with dimethyl acetylenedicarboxylate in THF to take place, but this result was attributed to catalysis of enol formation rather than direct involvement of the enolate in cycloaddition as proposed in the present study. See also ref 7. In the broader context of anion-influenced reactions, very recently Hart et al.[17] found that conversion of 2-H to 2-MgBr in a 1,3-diene led to an accelerated Diels–Alder reaction, and we[18] have also reported (arguably related) *de*celeration associated with a diene 1-H to 1-Li conversion.

(15) (a) Oku, A.; Kakihana, T.; Hart, H. *J. Am. Chem. Soc.* **1967**, *89*, 4554. (b) Papies, O.; Grimme, W. *Tetrahedron Lett.* **1980**, 2799. (c) Rajanbabu, T. V.; Eaton, D. F.; Fukunaga, T. *J. Org. Chem.* **1983**, *48*, 652.

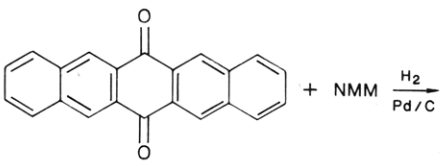
(16) Schultz, O. E.; Frey, G. *Arch. Pharm. (Weinheim)* **1977**, *310*, 776.

(17) Hart, H.; Du, C.-J. F.; Mohebalian, J. *J. Org. Chem.* **1988**, *53*, 2720.

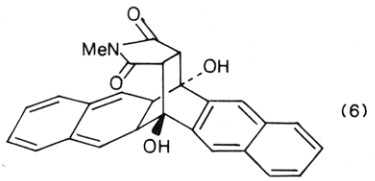
(18) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611.

(19) Hydroquinone itself reacts with diethyl fumarate (Nakazaki, M.; Naemura, K.; Yoshihara, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3278) and MA (Jefford, C. W.; Wallace, T. W.; Acar, M. *J. Org. Chem.* **1977**, *42*, 1654) but gives product derived from cycloaddition across the 2,5-positions of this 1,4-diol.

Naphthacenequinone reacts similarly to give bridgehead diol cycloadducts (exo, endo stereochemistry has not been determined). Interestingly, the procedure also extends to the pentacenequinone **10**, which affords the cycloadduct **11** when reduced in the presence of NMM.



10

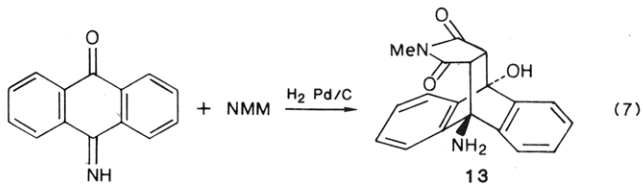


(6)

11

The monoimine[20] (**12**) of anthraquinone was prepared and subjected to in situ reduction–cycloaddition to give the novel aminoalcohol cycloadduct **13**. Preliminary results indicate that quinone–monoimines of higher benzologues can also be employed in this manner.

These reactions provide direct[21] access to bridgehead



(7)

12 **13**

alcohols and amines, in noteworthy room temperature Diels–Alder reactions. The magnitude of the observed rate enhancement encourages further efforts to design highly reactive dienes based on linear polycyclic aromatics. The free hydroxyl groups of the adducts will interfere with some functional group interconversions on the dienophile portion, and methods to convert the OH groups to protected forms are needed. This problem and the details of the cycloaddition mechanism require further study.

Acknowledgment. Support by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

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(20) Costa, A.; Riego, J. M.; Garcia-Raso, A.; Sinisterra, J. V. *Justus Liebigs Ann. Chem.* **1981**, 2085.

(21) Czarnik et al.[3] prepared the bridgehead diol and diaminoanthracene–ethyl acrylate cycloadducts by Diels–Alder reactions of 9,10-bis(trimethylsilyloxy)anthracene and 9,10-dinitroanthracene, respectively, followed by functional-group interconversions. There are advantages to both approaches, depending upon the desired application.

Studies Relating to the Synthesis of the Immunosuppressive Agent FK-506: Synthesis of the Cyclohexyl Moiety via a Group-Selective Epoxidation

Summary: The asymmetric synthesis of the cyclohexyl moiety of FK-506 is reported. The absolute stereogenicity of the target subunit was derived from the catalytic asymmetric synthesis of an epoxide by the method of Sharpless.

Sir: The discovery of compounds capable of preventing graft rejection following bone marrow and organ transplantation is an active area of immunological research. A goal of these activities is to selectively inhibit those subsets of host T cells that recognize the offensive donor MHC (major histocompatibility) antigens in order to prevent graft rejection without rendering the patient susceptible to opportunistic infections. The discovery of cyclosporin A (CsA), an agent utilized in clinical organ transplantation, represents one of the most significant advances in this area in the past decade.[1]

Recently, several disclosures have appeared detailing the potent immunosuppressive properties of the macrolide antibiotic FK-506 (**1**)[2] (Figure 1). The suppression of in vitro immune systems, including the inhibition of lymphokine production (IL-2, IL-3, IFN) was reported to take place at concentrations 100-fold lower than that required of CsA.[3] The results of in vivo studies involving renal

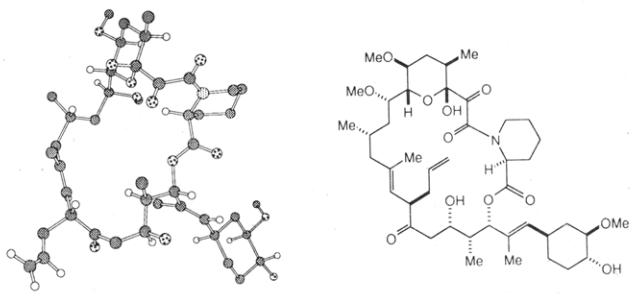

Figure 1. FK-506 (1).

allografting in the beagle dog[4] and cardiac allotransplantation in the rat[5] suggest a smaller dose requirement for FK-506 relative to CsA.

In addition to its role as a lead or candidate structure for clinical allotransplantation in humans, FK-506 serves as a new biological probe of the immune response. The recent discovery of an FK-506 binding protein[6] that is apparently related to the CsA binding protein cyclophilin[7] is illustrative. However, little is currently known con-

(1) Wenger, R. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 77.
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0022-3263/89/1954-0009$01.50/0